Atty. Docket No.: 3124-Z

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Richard J. Feldmann
Serial No. 09/866,925 Group Art Unit 1645
Filed: May 30, 2001 Examiner John S. Brusca
For: ALGORITHMIC DETERMINATION OF FLANKING DNA SEQUENCES THAT CONTROL THE EXPRESSION OF SETS OF GENES IN PROKARYOTIC, ARCHEA AND EUKARYOTIC GENOMES

#15/Dec. w/Spec.

DECLARATION UNDER 37 C.F.R. 1.132

Hon. Commissioner of Patents & Trademarks
Washington, D. C. 20231

Sir:

I, Richard W. Pastor, whose address is Laboratory of Biophysics, Center for Biologics Evaluation and Research, US Food and Drug Administration, 1401 Rockville Pike, Rockville MD, 20852-1448, declare as follows:

1. I received a Ph.D. degree in Biophysics from Harvard University. I also hold a MS degree in Chemistry from Syracuse University. My work experience includes 19 years (since Ph.D.) of research related to the computer simulation of biological systems, as well as supervision of related activities. I currently serve as Chief of the Laboratory of Biophysics in at the Center for Biologics Evaluation and Research, US Food and Drug Administration.

2. I have read the patent specification for application Serial No. 09/866,925 as filed in the United States Patent &

Trademark Office on May 30, 2001 for "ALGORITHMIC DETERMINATION OF FLANKING DNA SEQUENCES THAT CONTROL THE EXPRESSION OF SETS OF GENES IN PROKARYOTIC, ARCHEA AND EUKARYOTIC GENOMES." I read the amended claims submitted October 30, 2002, [and I have read the amended claims submitted with the amendment accompanying this Declaration]. I have read the official communication from the U.S. Patent & Trademark Office dated January 8, 2003. I have considered all of the claims.

3. I wish first to direct my comments to claims 20 - 27 which, I have been advised, are the broadest claims in the application. I have been also advised that claims 28 - 37 are all dependent from claim 20 and hence I am advised include the limitations of claim 20.

Claims 20 - 27 are as follows:

20. A method of identifying DNA sequences that control the expression of different collections of genes in a genome comprising detecting, by computer, one or more pairs of non-adjacent DNA sequences to which are bound one RNA molecule comprising of two RNA sequences.

21. A method of identifying DNA sequences that control the expression of different collections of genes in a genome comprising detecting, by computer, changes in connectron behavior in the genome as a function of changes in the sequence of the genome.

22. A method of modifying, by computer, the expression of different gene collections in a genome, comprising detecting changes in connectron behavior that results in changes in the level of connectron control sequences caused by an exogenous stimulus.

23. A method of detecting, by computer, where and when new genes have been integrated into a host genome comprising detecting the operable link between the newly introduced gene and the existing connectron behavior in said host genome.

24. A method of detecting, by computer, the expression effect of different gene collections in a given host genome, comprising detecting the transacting behavior of connectrons between the chromosomes thereof.

25. A method of modifying a given genome comprising modifying, by computer, the connectron organization therein.

26. A method of detecting, by computer, connectron control and target sequences in a given genome comprising:

determining the base composition of said genome,
determining one or more sites of control sequence organization, and/or
determining one or more sites of target application.

27. A method of determining, by computer, the response of a cell in any tissue to changes in the cell's environment and/or genetic composition comprising providing a complete genomic DNA sequence for the organism and determining the effect of changes in connectrons due to application of a given exogenous stimulus to the genome.

4. It should be noted that all of the claims, including the dependent claims, are directed to a tetradic relationship between two specific adjacent RNA single-stranded sequences (called C1 and C2 for control sequence 1 and control sequence 2) interact with two distant double-stranded DNA sequences (called T1 and T2 for target sequence 1 and target sequence 2). Claim 20 recites a method of identifying DNA sequences that control the expression of different collections of genes in a genome comprising detecting, by computer, one or more pairs of non-adjacent DNA sequences to which are bound one RNA molecule comprising of two RNA sequences.

5. I wish to state the following referring to pages 5 and 6

of the Examiner's action and in reference to subparagraphs a) through h):

In subpagraph a), the Examiner first states that in order to practice the claimed invention, one skilled in the art must identify and use a connectron to predict the relation of gene expression. Keeping in mind that the claims under consideration are directed to computer mediated methods of analysis of connectron sequences, I disagree with the Examiner's conclusion that there would be an unpredictable amount of experimentation required to practice the claimed invention.

The skilled practitioner would turn to the instant description and drawings for guidance in using the claimed invention. The specification provides a detailed roadmap for practicing the invention by one skilled in the art. Referring specifically to the specification and drawings, the introduction at pages 1 - 3 provides a basic description of connectron structure. Figures 1 - 3 are taken from the text by Alberts et al. entitled "The Molecular Biology of the Cell." Pages 3 - 25. Pages 26 - 36 provides a detailed description of a connectron structure. Page 31, the detailed description of the invention, provides a descriptive analysis of the flow diagrams utilized in the computer analysis of connectrons in any given genome. Additionally, ten samples of connectrons found by computer mediation are set out in the specification. Pages 39 - 56 give an example of a prokaryote connectron - E. coli. Hence, the algorithm is clearly defined and

could be programmed by a skilled scientist. In this sense, the amount of experimentation is quite predictable.

I agree that the nature of the invention, gene control, is complex, and that prior art does not discuss connectron symmetries; i.e., tt is my understanding and belief that the connectron invention disclosed in the instant application was made by the inventor, Richard J. Feldmann.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 6/5/03

(Signature)

Name: Richard W Paster

June, 2003

CURRICULUM VITAE

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Education:

1984 Ph.D. Harvard University, Biophysics
Dissertation Title: *Topics in Stochastic Dynamics of Polymers.* Preceptor: Martin Karplus

1977 M.S. Syracuse University, Chemistry
Thesis Title: *Surface Tension Calculations for Molten Salts: Critique and Modification of the Kirkwood-Buff Model.*
Preceptor: Jerry Goodisman

1973 B.A. Hamilton College, Major in Philosophy

Employment:

1996-Present Chief, Biophysics Laboratory, CBER/FDA

1998 Acting Chief, Laboratory of Immunobiochemistry, CBER/FDA

1990-1996 Research Chemist, Biophysics Lab, CBER/FDA

1984-1990 Senior Staff Fellow, Biophysics Lab, CBER/FDA

1984 Staff Fellow, Laboratory of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

Awards:

1997 *Center Director's Public Health Achievement Award*
Center for Biologics Evaluation and Research

1996 *Scientific Achievement - Senior Investigator*
Center for Biologics Evaluation and Research

1996 *Excellence in Science by a Group*
Food and Drug Administration

1977 *Teaching Assistant of the Year*
Department of Chemistry, Syracuse University

Research Area: The application of computer simulations and statistical mechanics to biophysics, with emphasis on membranes.

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Teaching:

1994 Adjunct Professor, George Mason University
Physical Biochemistry

1978-1980 Teaching Fellow, Harvard University
Physical Biochemistry and Introductory Biochemistry

1975-1977 Teaching Fellow, Syracuse University
General Freshman and Honors Freshman Chemistry

Publications

1. Resonance Raman Studies of Macrocyclic Complexes. 1. Structural and Electronic Effects in Synthetic Metal (II) Porphrin Analogues. W.H. Woodruff, R.W. Pastor and J.C. Dabrowiak, *J. Am. Chem. Soc.* **98**, 7999-8006 (1976).

2. Resonance Raman Studies of Macrocyclic Complexes. 2. Antiresonance and Selective Intensity Enhancement in Synthetic Metal (II) Porphrin Analogues, L.A. Nafie, R.W. Pastor, J.C. Dabrowiak and W.H. Woodruff, *J. Am. Chem. Soc.* **98**, 8007-8014 (1976).

3. Surface Tension Calculations for Molten Salts: Critique and Modification of the Kirkwood-Buff Model, R.W. Pastor and J. Goodisman, *J. Chem. Phys.* **68**, 3654-3666 (1978).

4. A Model for the Surface of a Molten Salt, J. Goodisman and R.W. Pastor, *J. Phys. Chem.* **82**, 2078-2081 (1978).

5. A Recognition Site in Synthetic Helical Oligonucleotides for Monoclonal Anti-Native DNA Autoantibody, David Stollar, Gerald Zon and Richard W. Pastor, *Proc. Natl. Acad. Sci. USA* **83**, 4469-2273 (1986).

6. Local Sequence Patterns of Hydrophobicity and Solvent Accessibility in Soluble Globular Proteins, David. J. Lipman, Richard W. Pastor and B. Lee, *Biopolymers* **26**, 17-26 (1987).

7. A Theoretically Determined Three-Dimensional Structure for the Repeating Tetrapeptide Unit of the Circumsporozoite Coat Protein of the Malaria Parasite Plasmodium falciparum, Bernard R. Brooks, Richard W. Pastor, Frederick W. Carson, *Proc. Natl. Acad. Sci. USA* **84**, 4470-4474 (1987).

8. The Parametrization of the Friction Constant for Stochastic Simulations of Polymers, Richard W. Pastor and Martin Karplus, *J. Phys. Chem.* **92**, 2636-2641 (1988).

9. Frictional Models for Stochastic Simulations of Proteins, Richard M. Venable and Richard W. Pastor, *Biopolymers* **27**, 1001-1014 (1988).

10. Brownian Dynamics Simulation of a Lipid Chain in a Membrane Bilayer, Richard W. Pastor, Richard M. Venable and Martin Karplus, *J. Chem. Phys.* **89**, 1112-1127 (1988).

11. A Simulation Based Model of NMR T_1 Relaxation in Lipid Bilayer Vesicles, Richard W. Pastor, Richard M. Venable, Martin Karplus, and Attila Szabo, *J. Chem. Phys.* **89**, 1128-1140 (1988).

Richard W. Pastor, Ph.D.

Publications (cont.)

12. An Analysis of the Accuracy of Langevin and Molecular Dynamics Algorithms, Richard W. Pastor, Bernard R. Brooks and Attila Szabo, *Mol. Phys.* **65**, 1409-1419 (1988).

13. Theoretically Determined Three-Dimensional Structures for Amphipathic Segments of the HIV-1 gp41 Envelope Protein, Richard M. Venable, Richard W. Pastor, Bernard R. Brooks and Frederick W. Carson, *AIDS Research and Human Retroviruses* **5**, 7-21 (1989).

14. Anisotropic Bead Models for Molecular Hydrodynamics, Richard W. Pastor and Robert Zwanzig, *J. Chem. Phys.* **90**, 5729-5734 (1989).

15. Inertial Effects in Butane Stochastic Dynamics, Richard W. Pastor and Martin Karplus, *J. Chem. Phys.* **91**, 211-218 (1989).

16. Determination of Chain Conformations in the Membrane Interior by Brownian Dynamics Simulations, Richard W. Pastor, in *Molecular Description of Biological Membrane Components by Computer Aided Conformational Analysis*, Vol. I, (ed. R. Brasseur, CRC Press, Boca Raton, 1990), pp. 171-201.

17. Model for the Structure of the Lipid Bilayer, Richard W. Pastor, Richard M. Venable and Martin Karplus, *Proc. Natl. Acad. Sci. USA* **88**, 892-896 (1991).

18. Mean Field Stochastic Boundary Molecular Dynamics Simulation of a Phospholipid in a Membrane, Hans De Loof, Stephen C. Harvey, Jere P. Segrest and Richard W. Pastor, *Biochemistry* **30**, 2099-2113 (1991).

19. Molecular Dynamics Simulation of Methyl Group Relaxation in Water, Goran Widmalm, Richard W. Pastor and T.E. Bull, *J. Chem. Phys.* **94**, 4097-4098 (1991).

20. Analyses of Statistical Errors in Dynamics Simulations, Richard W. Pastor, in *Proteins: Structure, Dynamics, Design* (ed. V. Renugopalakrishnan, P.R. Carey, I.C.P. Smith, S.G. Huang and A.C. Storer, ESCOM Science Publishers, The Netherlands, 1991), pp. 229-233.

21. Synexin: Molecular Mechanism of Calcium-Dependent Membrane Fusion and Voltage-Dependent Calcium Channel Activity, Harvey B. Pollard, Eduardo Rojas, Richard W. Pastor, Eduardo M. Rojas, H. Robert Guy, and A. Lee Burns, *Ann. New York Acad. Sci.* **635**, 328-351 (1991).

22. Langevin Dynamics of Peptides: the Frictional Dependence of Isomerization Rates of N-Acetylalanyl-N'-Methylamide, Richard J. Loncharich, Bernard R. Brooks and Richard W. Pastor, *Biopolymers* **32**, 523-535 (1992).

23. Backbone Dynamics of Calmodulin Studied by ^{15}N Relaxation Using Inverse Detected Two-Dimensional NMR Spectroscopy: The Central Helix is Flexible, Gaetano Barbato, Mitsuhito Ikura, Lewis E. Kay, Richard W. Pastor and Ad Bax, *Biochemistry* **31**, 5269-5278 (1992).

24. Conformational States of a TT Mismatch from Molecular Dynamics Simulation of d(CGCGATTCGCG), Richard M. Venable, Goran Widmalm, Bernard R. Brooks, William Egan and Richard W. Pastor, *Biopolymers* **32**, 783-794 (1992).

Richard W. Pastor, Ph.D.

Publications (cont.)

25. A Comparison of Langevin and Molecular Dynamics Simulations: Equilibrium and Dynamics of Ethylene Glycol in Water, Goran Widmalm and Richard W. Pastor, *J. Chem. Soc. Faraday Trans.* **88**, 1747-1754 (1992).

26. Langevin Dynamics of a Linear Rotor in a Maier-Saupe Potential: Kramers Turnover of the Flipping Rate, Richard W. Pastor and Attila Szabo, *J. Chem. Phys.* **97**, 5098-5100 (1992).

27. Positional Time Correlation Function for One-Dimensional Systems with Barrier Crossing: Memory Function Corrections to the Optimized Rouse-Zimm Approximation, Angelo Perico, Roberto Pratolongo, Karl F. Freed, Richard W. Pastor and Attila Szabo, *J. Chem. Phys.* **98**, 564-573 (1993).

28. Molecular Dynamics Simulations of a Lipid Bilayer and of Hexadecane: An Investigation of Membrane Fluidity, Richard M. Venable, Yuhong Zhang, Barry J. Hardy and Richard W. Pastor, *Science* **262**, 223-226 (1993).

29. Molecular and Stochastic Dynamics Simulation of Lipid Membranes, Richard W. Pastor and Richard M. Venable, in *Computer Simulation of Biomolecular Systems: theoretical and experimental applications* (ed. Wilfred F. van Gunsteren, Paul K. Weiner and Anthony K. Wilkinson, ESCOM Science Publishers, Leiden, 1993), pp. 443-463.

30. Conformational Sampling of Hydrocarbon and Lipid Chains in an Ordering Potential, Barry J. Hardy and Richard W. Pastor, *J. Comput. Chem.* **15**, 208-226 (1994).

31. A Comparison of Methods for Computing Transition Rates from Molecular Dynamics Simulation, Yuhong Zhang and Richard W. Pastor, *Mol. Sim.* **13**, 25-38 (1994).

32. Techniques and Applications of Langevin Dynamics Simulations, Richard W. Pastor, in *The Molecular Dynamics of Liquid Crystals* (eds. G.R. Luckhurst and C.A. Veracini, Kluwer Academic Publishers, The Netherlands, 1994), pp. 85-138.

33. Molecular Dynamics and Monte Carlo Simulations of Lipid Bilayers, Richard W. Pastor, *Current Opinion in Structural Biology* **4**, 486-492 (1994).

34. Method For Characterizing Transition Concertedness From Polymer Dynamics Computer Simulations, Michael L. Brown, Richard M. Venable and Richard W. Pastor, *Biopolymers* **35**, 31-46 (1995).

35. Constant Pressure Molecular Dynamics Simulation: The Langevin Piston Method, Scott E. Feller, Yuhong Zhang, Richard W. Pastor and Bernard R. Brooks, *J. Chem. Phys.* **103**, 4613-4621 (1995).

36. Computer Simulation of Liquid/Liquid Interfaces. I. Theory and Application to Octane/Water, Yuhong Zhang, Scott E. Feller, Bernard R. Brooks and Richard W. Pastor, *J. Chem. Phys.* **103**, 10252-10266 (1995).

Publications (cont.)

37. Computer Simulation of Liquid/Liquid Interfaces. II. Surface Tension-Area Dependence of a Bilayer and Monolayer, Scott E. Feller, Yuhong Zhang and Richard W. Pastor *J. Chem. Phys.* **103**, 10267-10276 (1995).

38. Rotational Diffusion Anisotropy of Human Ubiquitin from ^{15}N NMR Relaxation, Nico Tjandra, Scott E. Feller, Richard W. Pastor and Ad Bax, *J. Am. Chem. Soc.* **117**, 12562-12566 (1995).

39. Molecular Dynamics Simulations of Neat Alkanes: the Viscosity Dependence of Rotational Relaxation, Yuhong Zhang, Richard M. Venable and Richard W. Pastor, *J. Phys. Chem.* **100**, 2652-2660 (1996).

40. Time Scales of Lipid Dynamics and Molecular Dynamics, Richard W. Pastor and Scott E. Feller, in *Membrane Structure and Dynamics* (ed. K.M. Merz and B. Roux, Birkhauser, Boston, 1996), pp. 3-29.

41. On Simulating Lipid Bilayers with an Applied Surface Tension: Periodic Boundary Conditions and Undulations, Scott E. Feller and Richard W. Pastor, *Biophysical Journal* **71**, 1350-1355 (1996).

42. Diffusion Limited First Contact of the Ends of a Polymer: Comparison of Theory and Simulation, Richard W. Pastor, Robert Zwanzig and Attila Szabo, *J. Chem. Phys.* **105**, 3878-3882 (1996).

43. The Effect of Electrostatic Force Truncation on Interfacial and Transport Properties of Water, Scott E. Feller, Richard W. Pastor, Atipat Rojnuckarin, Steven Bogusz, and Bernard R. Brooks, *J. Phys. Chem.* **100**, 17011-17020 (1996).

44. The Length Scales of Lipid Dynamics and Molecular Dynamics, Scott E. Feller and Richard W. Pastor, in *Proceedings of the 1997 Pacific Symposium in Biocomputing*, (ed. R.B. Altman, A.K. Dunker, L.Hunter, T.E. Klein, World Scientific, Singapore, 1997), pp. 142-150.

45. Molecular Dynamics Simulation of Unsaturated Lipid Bilayers at Low Hydration: Parametrization and Comparison with Diffraction Studies, Scott E. Feller, Daxu Yin, Richard W. Pastor and Alexander D. MacKerell, Jr. *Biophysical Journal*, **73**, 2269-2279 (1997).

46. Computer simulation of a DPPC phospholipid bilayer: Structural Changes as a Function of Molecular Surface area, Scott E. Feller, Richard M. Venable and Richard W. Pastor, *Langmuir* **13**, 6555-6561 (1997).

47. Time Correlation Functions, Richard W. Pastor, in *Encyclopedia for Computational Chemistry* (ed. P.R. Schleyer, John Wiley & Sons, UK, 1998).

48. Solution Structure of the Linked Cell Attachment Modules of Mouse Fibronectin Containing the RGD and Synergy Regions: Comparison with the Human Fibronectin Crystal Structure, Valerie Copie, York Tomita, Steven K. Akiyama, Shin-ichi Aota, Kenneth M. Yamada, Richard M. Venable, Richard W. Pastor, Susan Krueger and Dennis A. Torchia *J. Mol. Biol.* **277**, 663-682 (1998).

Richard W. Pastor, Ph.D.

Publications (cont.)

49. Constant Surface Tension Simulations of Lipid Bilayers: the Sensitivity of Surface Areas and Compressibilities, Scott. E. Feller and Richard W. Pastor, *J. Chem. Phys.* **111**, 1281-1287 (1999).

50. Distinguishing Anisotropy and Flexibility of the Pentasaccharide LNF-1 in Solution by Carbon-13 NMR Relaxation and Hydrodynamic Modeling, Torgny Rundlöf, Richard M. Venable, Richard W. Pastor, Jozef Kowalewski and Göran Widmalm, *J. Am. Chem. Soc.* **121**, 11847-11854 (1999).

51. Statistical Considerations in the Establishment of Release Criteria for Allergen Vaccines, in *Proceedings of the 1999 Paul Ehrlich Symposium*, Jay E. Slater, Albert A. Gam, Maneesha D. Solanki, Suzann H. Burk, Faith M. May and Richard W. Pastor (ed. R. Kurth and D. Haustein, GIT VERLAG, Darmstadt, 2000), pp. 47-56.

52. The Determination of Equivalent Doses of Standardized Allergen Vaccines, Jay E. Slater and Richard W. Pastor, *J. Allergy and Clinical Immunology* **105**, 468-474 (2000)

53. The Stability of House Dust Mite Allergens in Glycerinated Extracts. Lyudmila N. Soldatova, Elizabeth J. Paupore, Suzann H. Burk, Richard W. Pastor and Jay E. Slater, *J. Allergy and Clinical Immunology* **105**, 482-488 (2000).

54. Molecular Dynamics Simulations of Gel ($L_{\beta I}$) Phase Lipid Bilayers in Constant Pressure and Constant Surface Tension Ensembles. Richard M. Venable, Bernard R. Brooks and Richard W. Pastor, *J. Chem. Phys.* **112**, 4822-4832 (2000).

55. Molecular Dynamics Simulations of Octyl Glucoside Micelles: Structural Properties, Stephen Bogusz, Richard M. Venable and Richard W. Pastor, *J. Phys. Chem. B* **104**, 5462-5470 (2000).

56. ICAM-1 Enhances MHC-peptide Activation of CD8+ T-cells without an Organized Immunological Synapse, Julia S. Goldstein, Trina Chen, Elena Gubina, Richard W. Pastor and Steven Kozolowski, *European J. Immunology*, **30**, 3266-3279 (2000).

57. Molecular Dynamics Simulations of Octyl Glucoside Micelles: Dynamic Properties, Stephen Bogusz, Richard M. Venable and Richard W. Pastor, *J. Phys. Chem. B* **105**, 8312-8321 (2001).

58. Molecular Dynamics Simulations of Water Wires and Water/Octane Model Systems, Richard M. Venable and Richard W. Pastor. *J. Chem. Phys.* **116**, 2663-2664 (2002).

59. Simulations of Membranes and Other Interfacial Systems Using $P2_1$ and Pc Periodic Boundary Conditions, Elizabeth A. Dolan Richard M. Venable, Richard W. Pastor and Bernard R. Brooks, *Biophysical Journal* **85**, 2317-2325 (2002).

60. Lipid Bilayers, NMR Relaxation, and Computer Simulations, Richard W. Pastor, Richard M. Venable, Scott E. Feller, *Accounts of Chemical Research* **35,** 438-446 (2002).

61. Micelle-Bound Conformation of a Hairpin-Forming Peptide: A Combined NMR and Molecular Dynamics Study. Ann M. Dixon. Richard M. Venable, Richard W. Pastor and T.E. Bull, *Biopolymers* **65**, 284-298 (2002).

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Publications (cont.)

62. Application of NMR, Molecular Simulation and Hydrodynamics to Conformational Analysis of Trisaccharides, Ann M. Dixon, Richard M. Venable, Göran Widmalm, T.E. Bull and Richard W. Pastor, *Biopolymers, in press.*

63. Sample Size Considerations for Establishing Clinical Bioequivalence of Allergen Formulations. in *Proceedings of the 2002 Paul Ehrlich Symposium*. Ronald L. Rabin, Jay E. Slater, Peter Lachenbruch, Richard W. Pastor, *in press*.

FDA Guidance Documents:

Testing Limits in Stability Protocols for Standardized Grass Pollen Extracts

Potency Limits for Standardized Dust Mite and Grass Allergen Vaccines: A Revised Protocol